Serial No. 09/702,944
Filed: October 31, 2000

Claims 12, 19-21, 25, 28 and 29 stand withdrawn from consideration.

Claims 1-11, 13-18, 22-24, 26, 27, 30 and 31 stand finally rejected.

Claims 10-13, 19-21, 24, 25, 28 and 29 are canceled without prejudice or disclaimer of subject matter.

Claims 1-4, 14 and 30 are amended.

Claims 1-4, 14 and 30 are amended to comply with, without acquiescing to, the election requirement made final by the Examiner. No new matter is added.

The present invention relates to azole compounds useful for the treatment of systemic mycoses and suitable for both oral and parenteral administration, a process for their manufacture, antifungal compositions containing them and a method for treating mycoses.

Applicants request reconsideration of pending claims 1-9, 14-18, 22, 23, 26, 27, 30 and 31 in light of the above claim amendments taken with along the following remarks.

Election / Restriction

In the spirit of compact prosecution, without acquiescing to the merits of the present requirement for restriction and election of species, Applicants have amended the claims, as suggested by the Examiner, without prejudice or disclaimer of the subject matter so canceled. Applicants retain the right to file divisional application(s) on the non-elected invention(s).

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Claim Rejections – 35 USC 112

Claims 1 and 2 stand rejected under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and/or use the invention. More specifically, the Examiner objects to the use of the expressions optionally substituted and substituted in the claims.

While not acquiescing to the merits of the rejection, Applicants have amended claim 1 to recite the specific substituents possible for the R^3 group, as described in the specification at pages 3 and 4. For this reason, reconsideration and withdrawal of the rejection of claims 1 and 2 as being rejected under 35 USC 112, first paragraph, is respectfully requested.

Claim Rejections – 35 USC 102

Claims 1-11, 13-18, 22-24, 26, 27, 30 and 31 stand rejected under 35 USC 102(e) and/or (f) as being anticipated by Hayase et al. (US 6,300,353). The Examiner urges that the reference specifically recites the instant compound. This rejection is technically and legally improper and should be withdrawn.

The instant claims are drawn, *inter alia*, to compounds having a structure substantially different from those disclosed in Hayase. The instant claims are drawn to compounds falling into the class of compounds known as carbamates (RR'NCOOR"). In contrast, Hayase discloses only substituted benzyl groups attached to the triazole. Thus, there is neither any teaching nor and fair suggestion of any carbamate-like compounds in

the Hayase patent. Furthermore, Hayase teaches only a benzyl group attached to the triazole ring. In the present invention there cannot be a benzyl group attached to the triazole.

The patent statute, under section 102 of 35 U.S.C., states, "A person shall be entitled to a patent unless – *the invention was* ...." (emphasis added) The statute requires the Examiner to compare the invention claimed by the Applicants to the prior art.

The compounds disclosed in Hayase clearly do not anticipate the compounds instantly claimed. The compounds instantly claimed are structurally different from those disclosed in Hayase. In efforts to better understand the Examiner's grounds for rejection, Applicants look toward the case law cited by the Examiner in her 102(e)/102(f) rejection (Marion Merrell Dow Inc. v. American Cyanamid Co., 36 USPQ2d 1036). The Dow case, however, is inapposite to the instant application.

Dow is a case asking whether a diltiazem precursor produced by a patent process is "materially changed" or converted to "trivial and nonessential component of another product" within the meaning of 35 USC 271(g) on a question of patent infringement. Section 271(g) pertains to infringement of a process patent. *See* Eli Lilly & Co. v. American Cyanamid Co., 82 F.2d 1568 (Fed. Cir. 1996) for a discussion of this statue by the Court of Appeals for the Federal Circuit. Section 271(g) of 35 U.S.C. states,

> (g) Whoever without authority imports into the United States or offers to sell, sells, or uses within the United States a product which is made by a process patented in the United States shall be liable as an infringer. ... A product which is made by a patented process will, for purposes of this title, not be considered to be so made after (1) it is materially changed by subsequent process; or (2) it becomes a trivial or non-essential component of another product.

The Examiner has pulled a quote, out of context, and has attempted to apply that statement to the instant case. More specifically, the Examiner states that "The precursor and final product are not different products, regardless of differences in their activity and efficacy" Office Action, at pages 3 and 4 (quoting Dow, 36 USPQ2d at 1039). This statement was true in the Dow case, when looking at the precursor and final product under the standards of infringement under 35 USC 271(g). The Dow case has no relevance whatsoever on issues of patentability, especially those which present themselves in the instant case.

Applicants are not blind, however, to the Examiner's perspective. It appears the Examiner has an issue with the fact that, in plasma, the carbamate compounds of the present invention convert into azole compounds, such as (2S, 3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol. See, for example, Table 2, bridging pages 32 and 33 of the specification. Some of these azole compounds are known in the art. The (2S, 3R)-3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol compound is, for example, disclosed in the Hayase patent.

Neither the patent statute nor any case law known to Applicants has stated that a claimed compound may be anticipated by a known metabolite thereof. Patents are frequently granted on pro-drug compounds. A quick search of the patent database found several issued patents that are pro-drugs of known pharmaceuticals (see, for example, U.S. patent nos. 6,407,235; 6,271,212; 5,696,126; 5,561,122; and 5,529,989). Pro-drug forms of known compounds are often invented to improve solubility, enhance delivery, or provide less toxic side effects. To deny patent protection on these novel chemical

entities, "pro-drug compounds" would stifle the very inventiveness that provides these improvements, thus creating a patentability standard that flies in the face of the purpose of the patent system, which is to promote the progress of science.

While Applicants respectfully submit that the above arguments clearly render the present claims neither anticipated nor obvious over Hayase, Applicants have gone further by previously supplying the declaration of Isao Umeda. The Umeda declaration shows that the antigenicity of the N-substituted carbamoyloxyalkyl-azolium derivatives of the present invention is negative while the antigenicity of the corresponding compounds of Hayase is positive.

In response to this declaration, the Examiner states that the declaration is of little, if any, probative value because it fails to include the final product and the elected compound. Applicants respectfully disagree. As to the elected compound, compound 2 of the declaration is clearly within the scope of compounds of the pending claims, as amended. As a matter of fact, compound 2 **is** the **exact** compound elected in Paper No. 6 on January 14, 2002. As to the 'final product', Applicants are assuming that the Examiner is referring to a product obtained from the contact of the claimed compound with plasma. However, this 'final product' is not claimed. Therefore, Applicants respectfully submit that the Umeda declaration clearly includes the compounds as instantly claimed.

The Examiner urges that the claims are directed to using the instant compounds for the treatment of fungicidal infections. Claim 31 is the only claim so drawn. The majority of the claims are drawn to compounds. The declaration is used to show

unexpected results obtained with the compounds of the present invention as compared to the closest compound disclosed by Hayase.

Finally, the Examiner states that the declaration is silent as to whether the compounds treat any fungal infection. Applicants have shown an unexpected decrease in toxicity from the compounds of Hayase to those of the instant invention. Unexpected results do not have to be shown in the method of treatment. As noted above, many pro-drugs are developed not only to enhance efficacy, but also to improve solubility and decrease toxicity. A showing of unexpected results in any aspect of the compounds is nonetheless a showing of unexpected results.

For the totality of reasons outlined above, the pending claims can not be anticipated by the Hayase patent. Reconsideration and withdrawal of the rejection of claims 1-11, 13-18, 22-24, 26, 27, 30 and 31 as being anticipated under 35 USC 102(e)/(f) is respectfully requested.

Claim Rejections – 35 USC 103

Claims 1-11, 13-18, 22-24, 26, 27, 30 and 31 stand rejected under 35 USC 103(a) as being unpatentable over Hayase in view of Hudyma et al. And Davidsen et al.

At the outset, the Examiner states that Hayase discloses the final product having the same use. For the reasons set out above, Applicants respectfully submit that Hayase neither teaches nor fairly suggests the compounds as claimed. Hudyama is relied upon to teach that analogous amine salts of triazoles similar to those claimed, and Davidsen is

relied upon to teach that pyridine salts are known to be extremely soluble. None of the cited references teach or fairly suggest the compounds as claimed.

To establish a *prima facie* case of obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). As discussed above, Applicants know of no statute of case law that supports the proposition that a novel compound that metabolizes in the body to a known compound is anticipated or rendered obvious by that known compound. Thus, the current record does not support a *prima facie* case inasmuch as there is no showing in the record that all the limitations of the claim are taught or suggested by the prior art.

For these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-11, 13-18, 22-24, 26, 27, 30 and 31 as being unpatentable under 35 USC 103(a).

Conclusion

In summary, Applicants respectfully submit that the instant application is in condition for allowance. Early notice to that end is earnestly solicited.

If a telephone conference would be of assistance in furthering prosecution of the subject application, applicants request that the undersigned be contacted at the number below.

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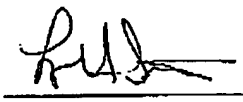
No fee is required in connection with the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,



Agent for Applicants
Lyman H. Smith
(Reg. No. 44,342)
340 Kingsland Street
Nutley, New Jersey 07110
Telephone: (973) 235-3916
Telefax: (973) 235-2363

127121

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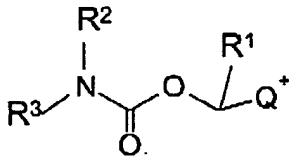
VERSION SHOWING CHANGES MADE

1. (Twice amended) A compound of the formula (I),



X- (I)

wherein

Q is a [3H-imidazole or 1,2,4-triazole derivative with antifungal activity] 3-[4-(4-cyanophenyl)thiazol-2-yl)]-2-(2,5-difluorophenyl)-1-(1H-1,2,4-triazol-1-yl)-butan-2-ol moiety which is linked to the remainder of the compound of formula (I) by a nitrogen in the azole;

R^1 is hydrogen or alkyl;

R^2 is hydrogen, alkyl, alkylcarbonyloxyalkyl, alkoxycarbonyl, alkylcarbonyl, mono- or dialkylaminoalkylcarbonyloxyalkyl;

R^3 is [alkylaminoalkyl, alkylcarbonyl, alkylcarbonyloxyalkyl, alkylaminoalkylcarbonyloxyalkyl, hydrogen, acylalkylaminoalkyl, alkyl, hydroxyalkyl, aminoalkyl, alkylcarbonylaminoalkyl, alkylcarbonylalkylaminoalkyl, alkoxycarbonylalkylaminoalkyl, alkoxycarbonylaminoalkyl, optionally substituted phenyl, optionally substituted] pyridin-2-yl or substituted pyridin-2-yl [optionally substituted 5- or 6-membered cycloalkyl, acylaminoalkyl, alkylaminoalkylacyloxyalkyl or the group (R^2, R^3)N- may form an optionally substituted pyrrolidine, pyrrolidone or piperidine]; and

X^- is a pharmaceutically acceptable anion,

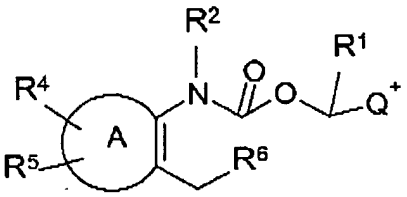
wherein

when R^3 is substituted pyridin-2-yl, the substituent is selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkyloxycarbonyl, cyano, trifluoromethyl, trifluormethoxy, nitro, aminosulfonyl, alkylaminocarboyloxyalkyl, sulfo, alkylcarbonyloxyalkyl and aminoalkylcarbonyloxyalkyl;

or a pharmaceutically acceptable salt thereof.

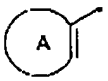
2. (Twice amended) Compounds of claim 1 wherein R^3 is [alkylaminoalkyl, alkylcarbonyl, alkylcarbonyloxyalkyl, alkylaminoalkylcarbonyloxyalkyl, substituted phenyl,] substituted pyridin-2-yl[or substituted 5-or 6-membered cycloalkyl].

3. (Amended) Compounds of claim 2 having formula (II),



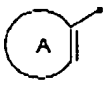
X^- (II)

wherein

R^1, R^2, Q, and X are as defined in claim 1; group 

is [phenyl or] pyridin-2-yl;

R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkyloxycarbonyl, cyano, trifluoromethyl, trifluormethoxy, nitro,

aminosulfonyl, alkylaminocarboyloxyalkyl, [and] sulfo [when group 

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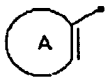
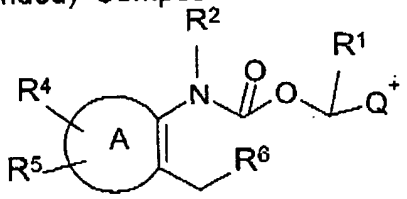
is phenyl or pyridin-2-yl and are in addition] , alkylcarbonyloxyalkyl [or] and

aminoalkylcarbonyloxyalkyl [when group  is pyridin-2-yl and are in

addition aminoalkylcarbonyl or alkylaminoalkyl when group  is phenyl]; and

R^6 is hydroxy, alkoxycarbonylalkylamino, alkoxycarbonylamino, amino, alkylamino, alkylcarbonyloxy, alkoxycarbonylalkylaminoalkylcarbonyloxy, alkoxycarbonylamino-alkylcarbonyloxy, alkylaminoalkylcarbonyloxy, aminoalkylcarbonyloxy, alkylcarbonylamino, alkylcarbonylalkylamino, acyloxy, acylamino, acylalkylamino.

4. (Amended) Compounds of claim 3 having formula (III),



X⁻ (III)

wherein

[R^1, R^2, Q, and X are as defined in claim 1;]

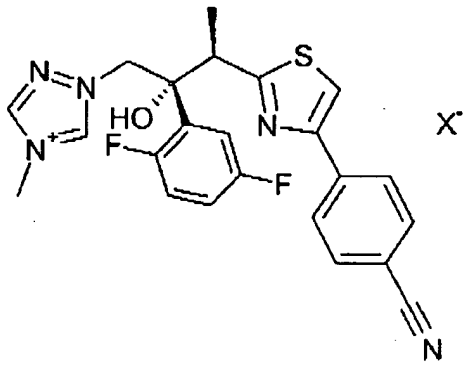
R^4 and R^5 are independently selected from the group consisting of hydrogen, halogen, alkyl, alkoxy, alkylthio, alkylsulfinyl, alkylsulfonyl, carboxy, alkyloxycarbonyl, cyano, trifluoromethyl, trifluoromethoxy, nitro, aminosulfonyl or sulfo; and

R^6 is hydroxy, alkoxycarbonylalkylamino, alkoxycarbonylamino, amino, alkylamino, alkylcarbonyloxy, alkoxycarbonylalkylaminoalkylcarbonyloxy, alkoxycarbonylamino-alkylcarbonyloxy, alkylaminoalkylcarbonyloxy,

aminoalkylcarbonyloxy, alkylcarbonylamino, alkylcarbonylalkylamino, acyloxy, acylamino, acylalkylamino[; and

group  is phenyl or pyridin-2-yl].

14. (Amended) Compounds of claim [13] 1 wherein Q is



as well as pharmaceutically acceptable salts, hydrates or solvates thereof.

30. (Twice amended) An pharmaceutical composition [for use as an antifungal,] comprising a compound of claim 1 and a pharmaceutically acceptable carrier.